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First synthesis of enantiomerically pure (1*S*,2*S*)- and (1*R*,2*R*)-1,2-diaminocyclobutanecarboxylic acid–ornithine derivative–, from racemic 2-aminocyclobutanone ☆

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ABSTRACT

An easy and efficient one-pot reaction from readily available 2-(*N*-Cbz) aminocyclobutanone selectively gave, by means of an asymmetric Strecker synthesis in the presence of a chiral benzylic amine, the thermodynamic 1,2-diamino nitriles. Basic hydrolysis, cleavage of the benzylic group and acidic hydrolysis of the resulting *trans*-1,2-diaminocyclobutanecarbonitrile gave, in a four-step sequence from the ketone, (1*S*,2*S*)- or (1*R*,2*R*)-1,2-diaminocyclobutanecarboxylic acid, ornithine derivatives. The absolute configuration has been established by X-ray analysis of the corresponding *trans*-diamino amide.

1. Introduction

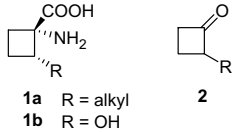
Conformationally constrained α- and β-amino acids have been incorporated into peptide surrogates to be used in structural and biomechanistic investigations as well as to obtain peptides with new or improved properties.[1,2] This incorporation increases the stability of these peptides towards chemical and enzymatic degradation. Hence, α,α-disubstituted α-amino acids are building blocks for the design and synthesis of new peptide hormones and enzyme inhibitors.[3] Furthermore, alicyclic α-amino acids such as the stereoisomeric 1-aminocyclopentane-1,3-dicarboxylic acids (ACPD) have been described as ligands at both the ionotropic and metabotropic glutamate receptors.[4]

On the other hand, β-amino acids, such as the neurotoxin β-*N*-methylamino-L-alanine (BMAA), are reported to function as modulators of the glycine binding site of the NMDA receptor complex.[5] In addition, β-peptides, the short oligomers of β-amino acids, can adopt all types of secondary peptide structures (helix, sheets and turns) and are considered as alternatives to α-amino acid oligomers since the β-peptide backbone offers greater opportunities for conformational rigidity than the α-peptides do.[6] Consequently, great interest for the synthesis and study of alicyclic α- and β-amino acids has rapidly increased,[2] in particular for cyclohexane,[7] cyclopentane[8] and cyclopropane[9] derivatives. However, amino acids from cyclobutane series have been little investigated.[10] In addition, the synthesis of substituted α-aminocyclobutanecarboxylic acids has not received the same amount of attention.[11] A few methods for 2-substituted α-amino acids have been described in recent years by means of asymmetric Strecker reactions;[12] by selective Michael-aldol reaction and by [2+2]-cycloaddition[13] or by alkylation of a glycine derivative.[14]

Conversely, for the synthesis of cyclobutane β-amino acids, three strategies have been reported: by Curtius rearrangement,[15] thermal cycloaddition[16] or photochemical [2+2]-cycloaddition.[17]

We reasoned that compounds bearing both the structural features of carbocyclic α-amino acids and of β-amino acids could be of considerable interest in various fields of medicinal chemistry.[18] The structural complexity of these molecules, having two vicinal chiral centres, also represented a challenge for their enantiopure synthesis. To the best of our knowledge, only a cyclohexane derivative of an α,β-diamino acid has recently been prepared by Frahm et al.[19] Cyclopentane analogues have been synthesized as 1-amino-2-nitro derivatives,[20] whereas the cyclobutane α,β-diamino acid–ornithine analogue[21] is still unknown.

We have previously reported on the asymmetric synthesis of cyclic analogues of naturally occurring α-amino acids from cyclopropanone acetals,[22] the α-amino-2-alkylcyclobutanecarboxylic acids **1a**[12b] and serine derivative **1b**[12c] from α-substituted cyclobutanones **2**, by means of an asymmetric Strecker reaction (Scheme 1).[23]



1a R = alkyl
1b R = OH
2

Scheme 1.

☆ Part of this study was previously reported at the Organic Chemistry Symposia at Palaiseau (SFC, September 2004) and at Chamonix Mont-Blanc (French-Japanese Symposium, September 2005), France.

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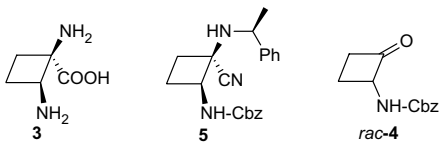
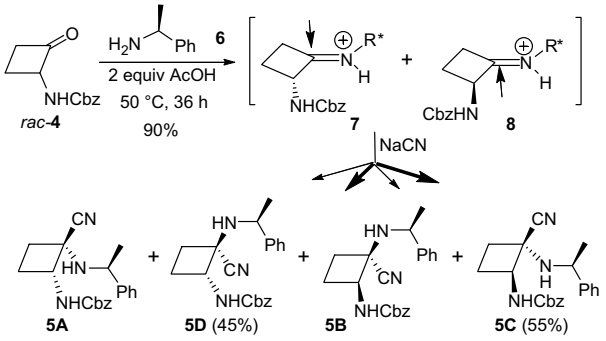
As part of our ongoing programme in this area, we herein report on the preparation of enantiopure 1,2-diaminocyclobutanecarboxylic acid **3** (ornithine analogue, c_4Orn)—in four steps—starting from the racemic 2-aminocyclobutanone **4** and a chiral benzylic amine as a chiral auxiliary, proceeding via amino nitrile **5** by an asymmetric Strecker reaction (Scheme 2).



Scheme 2.

2. Results and discussion

The racemic aminocyclobutanone *rac*-**4** was prepared from bis(trimethylsiloxy)cyclobutene according to Vederas (H_2N–Cbz, HCl gas) in 76% yield.[24] For the synthesis of the α-amino nitriles **5A**–**D**, the racemic cyclobutanone *rac*-**4** was subjected to a one-pot procedure previously developed in our group (Scheme 3).[12b,12c,22a] The standard one-pot reaction of cyclobutanone *rac*-**4** with (*S*)-α-methylbenzylamine **6** (2 equiv) was carried out in DMSO in the presence of 2 equiv of AcOH, and 1.5 equiv of NaCN at 50 °C for 3 days. We anticipated that under thermodynamic conditions as we have recently reported,[12c] the cyclobutanone condensation with the chiral auxiliary (*S*)-1-phenylethylamine **6** would give the corresponding iminiums **7** and **8**, which by the in situ addition of sodium cyanide to the C=N bond would predominantly afford two diastereomers of the four possible α-amino nitrile isomers **5A**–**D** (Scheme 3).

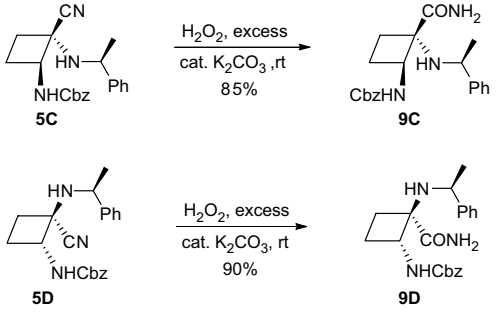


Scheme 3. Synthesis of α-amino nitriles **5A**–**D**.

Effectively, from cyclobutanone *rac*-**4** under thermodynamic control, only two major isomers **5C** and **5D** were isolated in a 55:45 ratio with an excellent yield. The more polar isomer on TLC is the amino nitrile **5D**. However, we are unable to isolate the kinetic isomers **5A** and **5B**. Taking into account the 90% yield and the 55:45 ratio, we can tentatively suppose that the equilibrium between the two iminiums **7** and **8** is not favoured,[12c] even though this type of iminium equilibrium has previously been reported in similar cyclopentane or cyclohexane systems.[25]

2.1. Basic hydrolysis

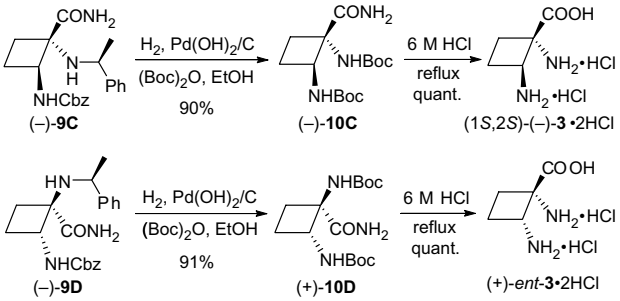
Subsequently, after straightforward silica gel column separation, the α -amino nitriles **5C** and **5D** were subjected to hydrolysis, separately[26] in DMSO in the presence of an excess of hydrogen peroxide (35 wt % in H_2O) and a catalytic amount of potassium carbonate at rt for 6 h,[27] to afford amides (1*S*,2*S*,1*S*)-**9C** and (1*R*,2*R*,1′*S*)-**9D** in good yields (85% and 90%, respectively). However, treatment of the nitrile **5C** with basic hydrogen peroxide (aq H_2O_2, KOH)[28] in EtOH only gave amide **9C** in 20% yield. Furthermore, acidic hydrolysis with concentrated H_2SO_4 in CH_2Cl_2 at 0 °C or rt led to a degradation of starting nitrile **5C** (Scheme 4).



Scheme 4.

Hydrogenolysis of pure α-aminocarboxamide **9C** was performed, as we have recently reported,[12c] with a catalytic amount of 20% $Pd(OH)_2$ on activated carbon (w/w 30%) in EtOH under hydrogen (1 atm, 10 h) in the presence of 3 equiv of di-*tert*-butylcarbonate [$(Boc)_2O$],[29] to simultaneously furnish, by a double cleavage and by in situ protection of free amines, the desired carbamate **10C** in excellent yield. Likewise, amide **9D** provided under the same conditions carbamate **10D** in 91% yield (Scheme 5).

The amino amides *trans*-**10C** and *trans*-**10D** were finally hydrolysed with 6 M HCl solution at reflux to furnish quantitatively, the 1,2-diaminocyclobutanecarboxylic acid hydrochlorides (1*S*,2*S*)-**3**·2HCl and (1*R*,2*R*)-*ent*-**3**·2HCl, respectively (Scheme 5).



Scheme 5.

2.2. Absolute configuration: X-ray crystallography

To determine the absolute configuration of all these molecules, we found that the amino amide **9D** gave suitable crystals. The X-ray crystallographic analysis showed,[30] as depicted in Figure 1, a (1*R*,2*R*,1′*S*)-absolute configuration of **9D**. Thus, the corresponding amino nitrile **5D** and the *N*-Boc amide **10D** should be (1*R*,2*R*,1′*S*) and (1*R*,2*R*), respectively. Consequently, nucleophilic attack of the cyanide anion, under thermodynamic conditions, occurred *syn* to the *N*-benzyloxycarbonyl group with an unlike approach to iminium **7** and via a thermodynamic–kinetic equilibrium (Scheme 6). This is in accordance with our very recently reported results, on the thermodynamic attack of cyanide on an iminium ion of a benzyloxycyclobutanone analogue.[12c] The same equilibrium could occur between amino nitriles **5B** and **5C** via iminium **8** (Schemes 3 and 6).

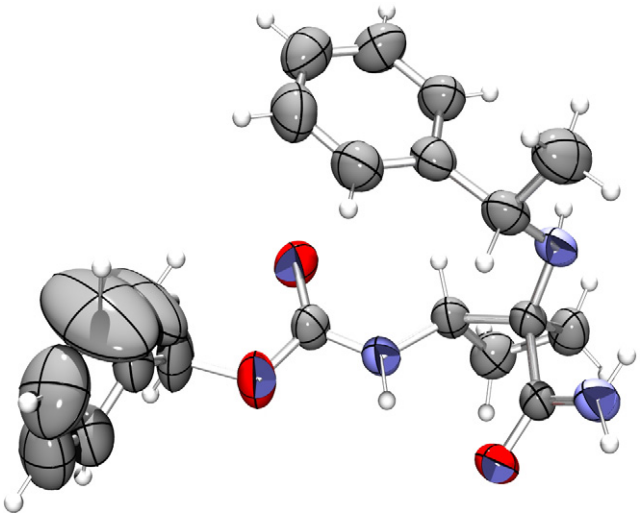
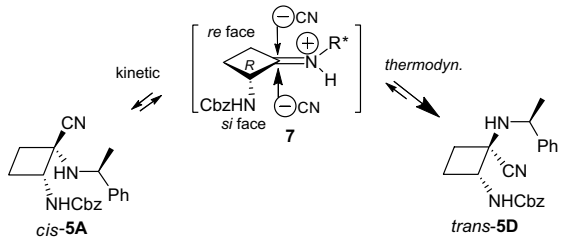


Figure 1. ORTEP plot of X-ray crystal structure of (1*R*,2*R*,1′*S*)-**9D**.



Scheme 6. Kinetic–thermodynamic equilibrium.

The amides **10D** and **10C**, presenting the same spectral data but giving the opposite specific rotation, are enantiomers. Consequently, the absolute configuration of **10C**, should be (1*S*,2*S*). Furthermore, it should be (1*S*,2*S*,1′*S*) for **9C** and (1*S*,2*S*,1′*S*) for **5C**.

3. Conclusion

We have developed an easy and efficient four-step synthesis of new, enantiopure 1,2-diamino-cyclobutanecarboxylic acids (−)-**3** and (+)-*ent*-**3**. Thus starting from readily available racemic 2-*N*-Cbz-cyclobutanone, we have demonstrated that the iminium ion formed from this ketone undergoes an asymmetric Strecker reaction to selectively give thermodynamic aminonitriles **5C** and **5D** in excellent yields. Subsequent basic hydrolysis of each nitrile furnished the corresponding amides **9C**–**D**, in good yields. The hydrogenolysis of the benzyl group of **9C**–**D** required treatment in the presence of Boc_2O to give the *N*-Boc derivatives **10C**–**D**. Finally, acidic hydrolysis provided the first optically active 1,2-diamino-cyclobutanecarboxylic acids **3** (c_4Ornithine derivatives) in good overall yields.

4. Experimental

4.1. General

The general experimental procedures and the analytical instruments employed have been described in detail in a previous paper.[22b]

4.1.1. *rac*-2-(*N*-Benzyloxycarbonyl)aminocyclobutanone (4)

rac-2-(*N*-Benzyloxycarbonyl)aminocyclobutanone **4** was prepared according to Vederas et al.[24]

4.2. General procedure A

To a solution of 2-(*N*-benzyloxycarbonyl)amino-cyclobutanone **4**[24] (2.45 g, 10.0 mmol), in DMSO (18 mL), were added successively AcOH (1.200 mL, 20.0 mmol), (*S*)-α-methylbenzylamine **6** (2.60 mL, 20.0 mmol) and NaCN (980 mg, 20.0 mmol). The mixture was stirred at 50–55 °C for 36 h. It was then diluted with EtOAc (100 mL), H_2O (10 mL) and basified to pH 9 with a saturated soln of $NaHCO_3$. The mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with water (5 mL), dried over $MgSO_4$, filtered and then concentrated under vacuum to give 4.40 g of the crudes amino nitriles as a mixture of two diastereoisomers. Purification by flash chromatography twice on silica gel (eluent: ether/CH_2Cl_2/petrol ether: 1:4:4 to 2:4:4) afforded 1.480 g (42.4%) of the less polar amino nitrile **5C**, 1.215 g (34.7%) of the polar amino nitrile **5D** and 450 mg (13%) as a mixture.

4.2.1. (1*S*,2*S*,1′*S*)-2-(*N*-Benzyloxycarbonyl)amino-1-(1′-phenylethyl)aminocyclobutanecarbonitrile, 5C

$[\alpha]_D = -181$ (*c* 1.00, $CHCl_3$); $R_f = 0.42$ (EtOAc/petrol ether: 3:7); IR (neat) *ν*: 3314, 3031, 2217 (C≡N), 1712 (NCOO), 1520, 1261; ^{1}H NMR ($CDCl_3$, 250 MHz): *δ* 1.20–1.55 (m, 2H, 2H–C_3), 1.41 (d, *J* = 6.4 Hz, 3H), 1.77 (dddd, *J* = 9.4, 10.5, 11.2, 11.2 Hz, 1H–C_4), 2.12 (dddd, *J* = 1.8, 8.5, 8.5, 10.5 Hz, 1H–C_4), 2.52 (br s, NH), 4.05 (q, *J* = 6.4 Hz, 1H–$C_{1'}$), 4.18 (ddd, *J* = 8.5, 8.5, 9.4 Hz, 1H–C_2), 5.15 (like AB system, *J* = 12.2, 22.2 Hz, 2H_{benzyl}), 5.32 (br d, *J* = 8.5 Hz, HNCO), 7.20–7.51 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): *δ* 23.2 (t, C_3), 24.6 (q, CH_3), 28.9 (t, C_4), 53.8 (t, $C_{1'}$), 56.0 (d, C_2), 64.1 (s, C_1), 67.3 (t, CH_2-Ph), 119.9 (C≡N), [12 arom. C: 127.6 (4C), 128.2 (1C), 128.3 (4C), 128.5 (1C), 136.0 (1C), 144.1 (1C)], 156.0 (NCOO); HRMS (EI) *m*/*z*: calcd mass for $C_{21}H_{23}N_3O_2$: 349.1790. Found: 349.1789.

4.2.2. (1*R*,2*R*,1′*S*)-2-(*N*-Benzyloxycarbonyl)amino-1-(1′-phenylethyl)aminocyclobutanecarbonitrile, 5D

$[\alpha]_D = -3.2$ and $[\alpha]_{365} = -23.6$ (*c* 1.00, $CHCl_3$); $R_f = 0.34$ (EtOAc/petrol ether: 3:7); IR (neat) *ν*: 3315, 3063, 2220 (C≡N), 1712 (NCO), 1520, 1261; ^{1}H NMR ($CDCl_3$, 360 MHz): *δ* 1.35 (d, *J* = 6.5 Hz, 3H, CH_3), 1.84–2.10 (m, 2H, H_{cycle}), 2.10–2.53 (m, 3H, 2H_{cycle} and NH), 4.08 (q, *J* = 6.5 Hz, 1H–$C_{1'}$), 4.19 (ddd, *J* = 9.0, *J* = 8.6, *J* = 7.5 Hz, 1H, H–C_2), 5.06 (AB system, J_{AB} = 12.3 Hz, 2H, CH_2O), 5.23 (d, *J* = 7.5 Hz, 1H, $H_{carbamate}$), 7.15–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): *δ* 23.6 (C_3), 23.7 (CH_3), 29.8 (C_4), 54.3 ($C_{1'}$), 55.8 (C_2), 63.1 (C_1), 67.2 (O–CH_2), 119.6 (C≡N), [12 arom. C: 126.8 (2C), 127.6 (2C), 128.2 (1C), 128.3 (1C), 128.6 (2C), 128.7 (2C), 136.0 (s), 144.7 (s)], 155.6 (OCON); HRMS (EI) *m*/*z*: calcd mass for $C_{21}H_{23}N_3O_2$: 349.1790. Found: 349.1786.

4.3. Amide formation from nitrile: general procedure B

To a solution of amino nitrile **5** (620 mg, 1.776 mmol) in DMSO (7 mL), were added K_2CO_3 (200 mg, 1.45 mmol) and an excess amount of H_2O_2 (2.8 mL, 31.7 mmol, 35 wt % in water).[27] The mixture was stirred at 0 °C for 1 h and at rt for 6 h. Complete elimination of excess of peroxide was performed by the addition of an aqueous saturated soln of $Na_2S_2O_3$ (negative KI test). The resulting mixture was extracted with EtOAc (3 × 100 mL). The organic layers were dried over $MgSO_4$, filtered and then concentrated under vacuum, to give after FC (silica gel, 15 g) the desired amide **9**.

4.3.1. (1*S*,2*S*,1′*S*)-2-(*N*-Benzyloxycarbonyl)amino-1-(1′-phenylethyl)amino-cyclobutanecarboxamide, 9C

Prepared according to procedure B: From nitrile **5C** (700 mg, 2.0 mmol), K_2CO_3 (220 mg, 1.60 mmol), H_2O_2 (3.00 mL, 34.0 mmol, 35 wt % in H_2O), in DMSO (10 mL). After stirring for 6 h and FC

(eluent: EtOAc/CH_2Cl_2: 20:80→25:75), we isolated 625 mg (85%) of amide **9C** as a white solid.

$[\alpha]_D = -53.0$ (c 1.00, $CHCl_3$); mp 36.6 °C; $R_f = 0.31$ (EtOAc/CH_2Cl_2: 10:90); IR (neat) ν: 3445, 3320, 3031, 1709 (NCOO), 1673 (CON), 1544, 1264; ^{1}H NMR ($CDCl_3$, 360 MHz, 320 K): δ 1.35 (d, $J = 6.5$ Hz, 3H, CH_3), 1.40–1.60 (m, 1H, H_{cycle}), 1.87 (br s, NH), 1.95–2.05 (m, 1H, H_{cycle}), 2.05–2.26 (m, 2H, H_{cycle}), 3.84 (q, $J = 6.5$ Hz, 1H–$C_{1'}$), 4.22 (m, 1H, H–C_2), 5.13 (br s, 2H, CH_2Ph), 5.24 (br s, 1H, NH_{amide}), 6.07 (br s, 1H, $H_{carbamate}$), 6.87 (br s, $1H_{amide}$), 7.10–7.38 (m, 10H); ^{1}H NMR ($CDCl_3$, 300 MHz) (two rotamers a/b, 73:27): δ 1.15:1.33 (d, $J = 6.6$ Hz, 3H, CH_3, a/b), 1.36–1.57 (m, 1H, H_{cycle}, a/b), 1.90 (br s, NH, a/b), 1.80–2.32 (m, 3H, H_{cycle}, a/b), 3.76:3.82 (q, $J = 6.6$ Hz, 1H–$C_{1'}$, b/a), 3.96:4.20 (ddd, $J = 9.7$ Hz, $J = 9.6$ Hz, $J = 9.5$ Hz, 1 H, H–C_2, b/a), [4.98 (d, $J = 11.7$ Hz, 1H, H_{benzyl}, b), 5.16 (d, $J = 11.7$ Hz, 1H, H_{benzyl}, b)], 5.13 (AB system, $J_{AB} = 12.3$ Hz, br s, 2H, CH_2Ph, a), 5.37:5.46 (br s, 1H, NH_{amide}, b/a), 6.31:6.51 (d, $J = 9.6$ Hz, 1H, $H_{carbamate}$, a/b), 6.88:6.95 (br s, $1H_{amide}$, b/a), 7.03–7.50 (m, 10H, a/b); ^{13}C NMR ($CDCl_3$, 62.9 MHz, 320 K): δ 23.7 (t, C_3), 24.7 (q, CH_3), 26.4 (t, C_4), 54.7 (d, $C_{1'}$), 55.6 (d, C_2), 66.7 (t, OCH_2), 69.9 (s, C_1), [12 arom. C: 126.4 (2C), 127.2 (1C), 128.1 (2C), 128.2 (1C), 128.5 (4C), 136.4 (s), 145.7 (s)], 155.6 (s, COO), 177.3 (s, CON); ^{13}C NMR ($CDCl_3$, 90.56 MHz) (two rotamers a/b, 73:27): δ 23.4:22.6 (t, C_3, a/b), 24.6:23.7 (q, CH_3, a/b), 26.0:23.4 (t, C_4, a/b), 54.9 ($C_{1'}$), 56.1 (C_2), 66.9:67.0 (OCH_2, a/b), 70.3:70.4 (C_1, a/b), [12 arom. C: 126.6 (2C), 127.3 (2C), 128.3 (1C), 128.4 (1C), 128.6 (4C), 136.5 (s), 146.1 (s)], 155.9:156.6 (COO, a/b), 177.4 (CON); HRMS (EI) m/z: calcd mass for $C_{21}H_{25}N_3O_3$: 367.1890. Found: 367.1888.

4.3.2. (1*R*,2*R*,1′*S*)-2-(*N*-Benzyloxycarbonyl)amino-1-(1′-phenylethyl)aminocyclobutanecarboxamide, 9D

Prepared according to procedure B: From nitrile **5D** (620 mg, 1.776 mmol), K_2CO_3 (200 mg, 1.45 mmol), H_2O_2 (2.80 mL, 31.7 mmol, 35 wt % in H_2O), in DMSO (7 mL). After stirring for 3 h and purification by FC (eluent: CH_2Cl_2 then EtOAc/CH_2Cl_2: 20:80), we isolated 585 mg (90%) of amide **9D** as colourless crystals used for X-ray diffraction.

$[\alpha]_D = -15.4$, $[\alpha]_{365} = -67.6$ (c 1, $CHCl_3$); mp 150.2 °C; $R_f = 0.31$ (EtOAc/CH_2Cl_2: 10:90); IR (neat) ν: 3446, 3322, 3031, 1710 (COO), 1671 (CON), 1502, 1263, 733; ^{1}H NMR ($CDCl_3$, 250 MHz, 320 K): δ 1.33 (d, $J = 6.7$ Hz, 3H), 1.58–1.65 (m, $1H_{cycle}$), 1.83 (s, NH), 1.92–2.11 (m, $1H_{cycle}$), 2.11–2.32 (m, $2H_{cycle}$), 4.04 (q, $J = 6.7$ Hz, H–$C_{1'}$), 4.33 (ddd, $J = 9.5$, 10.2, 10.0 Hz, 1H–C_2), 5.09 (s, 2H, $2H_{benzyl}$), 5.17 (br s, H_{amide}), 6.11 (d, $J = 10.2$ Hz, H–NCbz), 7.12 (br s, H_{amide}), 7.16–7.42 (m, 10H); ^{1}H NMR ($CDCl_3$, 250 MHz) (two rotamers a/b, 90:10): δ 1.31 (d, $J = 6.5$ Hz, 3H, CH_3), 1.62–1.80 (m, $1H_{cycle}$), 1.86 (s, NH), 1.94–2.44 (m, 3H, H_{cycle}), 4.04 (q, $J = 6.5$ Hz, H–$C_{1'}$), 4.33 (ddd, $J = 9.7$, 10.2, 10.0 Hz, 1H–C_2), 5.00–5.22 (br s, AB system, 2H, $2H_{benzyl}$), 5.54:5.93 (br s, H_{amide}, a/b), 6.37:6.88 (d, $J = 9.7$ Hz, H–Ncbz, a/b), 7.26:7.08 (br s, 1H, H_{amide} a/b), 7.20–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 90.56 MHz) (two rotamers a/b, 90:10): δ 23.8:23.3 (C_3, a/b), 24.3:24.9 (CH_3, a/b), 27.9:26.4 (C_4, a/b), 53.9 (C_2), 54.6:55.8 ($C_{1'}$, a/b), 66.6:66.9 (OCH_2, a/b), 69.5:69.9 (C_1, a/b), [12 arom. C: 126.6 (3C), 127.2 (1C), 128.1 (2C), 128.5 (1C), 128.6 (3C), 136.6 (s), 145.8 (s)], 155.6 (COO), 178.0 (CON); ^{13}C NMR ($CDCl_3$, 62.9 MHz, 320 K): δ 23.6 (t, C_3), 24.1 (q, CH_3), 27.7 (t, C_4), 53.7 (d, C_2), 54.4 (d, $C_{1'}$), 66.4 (t, OCH_2), 69.3 (s, C_1), [12 arom. C: 126.4 (2C), 127.0 (1C), 127.9 (2C), 128.1 (1C), 128.4 (4C), 136.4 (s), 145.6 (s)], 155.4 (COO), 177.8 (CON); HRMS (EI) m/z: calcd mass for $C_{21}H_{25}N_3O_3$: 367.1890. Found: 367.1889; Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.29; H, 6.51; N, 11.59.

4.3.2.1. X-ray structure analysis of (−)-90.[30] Crystal data for (−)-(1*R*,2*R*,1′*S*)-**9D**: Colourless crystal of 0.13 × 0.11 × 0.07 mm. $C_{21}H_{25}N_3O_3$, $M = 367.44$: orthorhombic system, space group $P2_12_12_1$ (No. 19), $Z = 4$, with $a = 8.712(5)$, $b = 12.110(5)$, $c = 19.141(5)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2019.42(15)$ Å^3, $d = 1.209$ g cm^{-3}, $F(000) = 784$, $\lambda = 0.71069$ Å (Mo-Kα), $\mu = 0.082$ mm^{-1}; 4622 reflections measured ($-11 \leqslant h \leqslant 11$, $-15 \leqslant k \leqslant 15$, $-24 \leqslant l \leqslant 24$), on a Bruker X8 diffractometer. The structure was solved and refined with SHELXL-97.[31] Hydrogen atom riding, refinement converged to $R(gt) = 0.0553$ for the 3131 reflections having $I > 2\sigma(I)$, and $wR(gt) = 0.1306$, Goodness of Fit $S = 1.017$, residual electron density: −0.149 and 0.173 e Å^{-3}.

4.4. Hydrogenolysis procedure

4.4.1. (1*S*,2*S*)-1,2-Di-[(*N*-*tert*-butyloxycarbonyl)amino]-cyclobutanecarboxamide, (−)-10C

To a solution of amino amide **9C** (185 mg, 0.50 mmol) in 7 mL of EtOH, were added Boc_2O (330 mg, 1.50 mmol) and 20% of Pd(OH)$_2$/C (Pearlman's catalyst, 100 mg). The mixture was stirred under 1 atm of H_2 at room temperature for 18 h (reaction monitored by TLC). The mixture was degassed under a stream of argon, filtered through a 2-cm-pad of Celite®, and washed with EtOH (2 × 10 mL). The combined filtrate and washings were concentrated and purified by FC (eluent: MeOH/CH_2Cl_2: 2:98→4/96). We isolated 148 mg (90%) of dicarbamate amide **10C** as a white yellow solid.

$[\alpha]_D = -15$ (c 0.25, $CHCl_3$); mp 176 °C; $R_f = 0.55$ (MeOH/CH_2Cl_2: 10:90); IR (neat) ν: 3437, 3332, 3206, 1710 (NCOO), 1669 (CON), 1366, 1169; ^{1}H NMR ($CDCl_3$, 250 MHz), (two rotamers a/b): δ 1.38:1.41 (s, 18H, a/b), 1.60–1.94 (m, $1H_{cycle}$, a/b), 1.94–2.35 (m, $2H_{cycle}$, a/b), 2.77 (m, like t, $1H_{cycle}$, a/b), 4.09/4.25 (m, 1H–C_2, a/b), 5.85 (br s, 1H–N, a/b), 5.92–6.15 (m, 1H–N, a/b and NH, a), 6.24–6.51 (m, NH, a/b), 7.17 (br s, NH, b); ^{13}C NMR ($CDCl_3$, 62.9 MHz), (two rotamers a/b): δ 22.2:23.1 (C_3, a/b), 26.6:27.3 (C_4, b/a), 28.2:28.3 (C–(CH_3)$_3$, b/a), 53.5:53.7 (C_2, a/b), 65.1:65.8 (C_1, b/a), 79.95:80.3 (C–(CH_3)$_3$, a/b), 154.3 (NCOO, a/b), 156.1 (NCOO, a/b), 174.6 (CON, a/b); HRMS (EI) m/z: calcd mass for $C_{15}H_{21}N_3O_5$: 352.1848. Found: 352.1848.

4.4.2. (1*R*,2*R*)-1,2-Di-[(*N*-*tert*-butyloxycarbonyl)amino]-cyclobutanecarboxamide, 10D

Prepared according to procedure of hydrogenolysis (as for preparation of **10C** from amide **9C**): From amino amide **9D** (295 mg, 0.800 mmol), Boc_2O (525 mg, 2.40 mmol), 20% of Pd(OH)$_2$/C (150 mg) in EtOH (6 mL). After 18 h at room temperature and purification by FC (eluent: MeOH/CH_2Cl_2: 2:97→3:96), we isolated 240 mg (91%) of dicarbamate amide (1*R*,2*R*)-**10D** as a white solid. $[\alpha]_D = +15$, and $[\alpha]_{365} = +60$ (c 0.25, $CHCl_3$); $[\alpha]_D = +9.6$, and $[\alpha]_{365} = +58$ (c 0.40, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz), (two rotamers a/b): δ 1.42:1.43 (s, 18 H, a/b), 1.60–1.92 (m, 1H–C_3, a/b), 1.95–2.33 (m, $2H_{cycle}$, a/b), 2.64–2.85 (m, 1H–C_4, a/b), 4.12 (m, 1H–C_2, a/b), 5.38 (br s, 1H–N, a/b), 5.48 (br s, 1H–N, a/b), 5.80:5.93 (br s, 1H–N, a/b), 6.33:6.60 (br s, NH, a/b); ^{13}C NMR ($CDCl_3$, 90.56 MHz), (two rotamers a/b): δ 22.2:23.1 (C_3, a/b), 26.8:27.5 (C_4, b/a), 28.3:28.4 (C–(CH_3)$_3$, b/a), 53.6:53.9 (C_2, a/b), 65.2:66.0 (C_1, b/a), 80.1:80.4 (C–(CH_3)$_3$, b/a), 154.4 (NCOO, a/b), 156.2 (NCOO, a/b), 174.9 (CON, a/b). All spectral data are identical with those reported for its antipode (1*S*,2*S*)-**10C**.

4.5. (1*S*,2*S*)-1,2-Diaminocyclobutanecarboxylic acid·hydrochloride, 3·2HCl

A solution of dicarbamate amide **10C** (82 mg, 0.25 mmol) in 6 M aq HCl (4.0 mL) was heated at reflux for 9 h. After cooling to room temperature, water (3 mL) was added and the resulting solution was washed with ether (4 mL). The aqueous layer was concentrated to dryness, then the solid residue was washed successively with EtOAc (2 mL) and ether (2 mL), to give 19 mg (quantitatively)

of the crude amino acid (1*S*,2*S*)-**3**·2HCl as a pale yellow solid. $[\alpha]_D = -4$ (*c* 0.60, H_2O); mp 210 °C decomp.; IR (KBr) *ν*: 3429, 3152, 1735 (COO), 1402, 1246; ^1H NMR (D_2O, 250 MHz, HOD: 4.80 ppm): δ 1.60–3.00 (m, $4H_{cycle}$), 4.46 (m, 1H–C_2); ^{13}C NMR (D_2O, 62.86 MHz): δ 26.9 (C_3), 29.4 (C_4), 49.6 (C_2), 57.6 (C_1), 169.2 (COO); HRMS data were not obtained.

4.5.1. (1*R*,2*R*)-1,2-Diaminocyclobutanecarboxylic acid·hydrochloride, *ent*-3·2HCl

Prepared from **10D** as noted above: $[\alpha]_D = +4.8$ (*c* 0.50, H_2O); mp 214 °C decomp. ^1H NMR (D_2O, 360 MHz, HOD: 4.80 ppm): δ 1.60–2.90 (m, $4H_{cycle}$), 4.46 (m, 1H–C_2); All spectral data are identical with those reported for its antipode (1*S*,2*S*)-**3**·2HCl.

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